ARCHIVES OF DISEASE IN CHILDHOOD

Leading article

Can we use methadone for analgesia in neonates?

The use of methadone analgesia is undergoing a revival in the field of pain management with doctors, nurses, and other healthcare professionals realising its potential advantages over other commonly used opioid analgesics.[1–3] The efficacy of methadone analgesia is well documented in adults, but limited information is available about the use of methadone in younger patients, particularly neonates. Painful experiences in neonates range from all newborns receiving routine vitamin K injections at birth to the critically ill preterm neonates who may experience up to 488 painful procedures during their stay in neonatal intensive care units.[4 5] The idea that neonates do not experience pain has long been refuted, and doctors are now more likely to administer routine pain relief.[6] The provision of adequate analgesia and sedation has been proved to maintain physiological stability and improve clinical outcomes in these patients.[7] Neonates undergoing surgery often need to be intubated and ventilated for prolonged periods after the operation. Most neonatal intensive care units use opioids such as fentanyl or morphine for sedation/analgesia for these and other critically ill infants requiring ventilatory support.[8 9] In this article, we report clinical problems associated with the routine use of these drugs and propose the potential benefits of using methadone as an alternative analgesic.

Opioid tolerance and adverse effects

Fentanyl is the most commonly used analgesic drug in the neonatal intensive care unit. It is a potent, rapid acting, synthetic opioid with a relative lack of haemodynamic side effects.[10] As a result of its short duration of action, fentanyl is given as a continuous infusion, thus requiring the need for intravenous access and additional quantities of intravenous fluid in critically ill neonates. Immature renal function and the incidence of congestive heart failure, particularly in preterm neonates with a patent ductus arteriosus, may result in potentially deleterious consequences from the additional fluid intake.

Other side effects of opioids are well known and include respiratory depression, decreased gastrointestinal motility, hypotension, and urinary retention. Adverse effects reported with the use of fentanyl also include chest wall rigidity and temperature instability.[11] Another complication associated with opioid use is the development of tolerance and physical dependence, leading to opioid withdrawal after discontinuation of the drug. Clinical studies have found that continuous infusions of fentanyl and morphine produce a high rate of opioid withdrawal when administered to critically ill infants.[12 13] This occurs more often with fentanyl than morphine.[13] Tolerance and physical dependence are thought to develop more rapidly with shorter acting drugs—for example, fentanyl—and after continuous infusions rather than with intermittent administration, perhaps because of longer receptor occupancy.[14] The metabolism of morphine in preterm neonates may further accelerate the development of opioid tolerance. Morphine is preferentially metabolised to morphine-3-glucuronide in the immature liver, leading to biliary excretion and reabsorption from the small intestine.[15 16] The effects of morphine-3-glucuronide are antianalgesic (also noted in adults[17]), thereby antagonising the therapeutic effects of morphine and contributing to the development of tolerance.

The analgesic efficacy of methadone can be explained by the signal transduction mechanisms mediating its μ-opioid agonist activity (L-methadone only) and non-competitive antagonism of *N*-methyl-D-aspartate (NMDA) receptors (both enantiomers, D- and L-methadone).[18 19] Recent in vitro studies suggest that methadone causes desensitisation of the μ-opioid receptor[20] by uncoupling the receptor from its underlying G-protein,[21] which appears to be mediated by protein kinase C-dependent phosphorylation. Activity of the δ-opioid receptor is critical for the development of morphine induced tolerance and dependence, and therefore concomitant exposure to both morphine and methadone suppresses the mechanisms leading to opioid tolerance.[21 22] Thus a rationale for the use of methadone analgesia can be supported by its specific μ-opioid effects, desensitisation of δ-opioid receptors, prolonged duration of action, and its antagonism at the NMDA receptor.

Use of methadone in adults

Methadone was first discovered by the Germans in the second world war, but its role as an effective analgesic drug was not described until a few years later.[23] Since then methadone has been mainly used as a maintenance drug to prevent withdrawal in opiate addicted adults. The negative connotation of methadone as a "drug for addicts", perceived by some members of the general public, may be one of the reasons why its usefulness as a potent analgesic agent has been ignored.[1]

Methadone is a long acting synthetic opioid with excellent bioavailability by the enteral route (> 90% in most patients), with documentation of its use by the sublingual, rectal, subcutaneous, intravenous, intramuscular, epidural, and intrathecal routes as well.[1] It is also considerably cheaper than other opioids and has a low incidence of side effects in adults. The prolonged half life of methadone (54 (20) hours; mean (SD)) enables its use as a single daily dose to prevent withdrawal symptoms in opiate addicts or for prolonged postoperative analgesia in adults.[24] A double blind randomised trial compared the intraoperative use of 20 mg intravenous morphine or methadone followed by supplemental doses of 5 mg to treat postoperative pain. The first supplementary dose was required at six hours after surgery in the group receiving morphine and at 21 hours in the group receiving methadone. Furthermore patients required significantly less methadone than morphine throughout their hospital stay with a comparable quality of pain relief in the two treatment groups.[25] Other studies have reported similar results confirming prolonged postoperative analgesia because of sustained therapeutic plasma levels resulting from the long half life of methadone.[24 26]

Use of methadone in children

Methadone has been used for the same clinical indications in children. Shir *et al*[27] reported that oral methadone was used in hospitals for treating severe pain in children, whereas Tobias *et al*[28 29] reported its use for the treatment of opioid dependence. After its successful use for opioid analgesia in over 70 children with severe and persistent pain, Shir *et al* recommended the use of methadone as a first line opioid when non-opioid medications fail to achieve adequate pain relief in children. Oral methadone treatment provides potent analgesia, rapid onset of action, prolonged clinical effects, high enteral bioavailability, minimal side effects, and low cost. Methadone was used in patients with opioid tolerance and withdrawal because of its safety and prolonged duration of action.[29] Methadone is used widely for the treatment of opioid withdrawal in neonates and children, based on clinical experience and repeated recommendations for its use,[14 30] although there are few data on its efficacy, safety, or pharmacokinetics in children.

One previous study on methadone pharmacokinetics in children aged 1–18 years, reported only in abstract form, found a prolonged elimination half life (19.2 (13.6) hours) with a range of 3.8–62 hours in these patients.[31] The variability of these data suggest that some paediatric patients may metabolise methadone as adults do, whereas others may have low plasma clearance rates. Berde *et al*[32] also investigated the duration of postoperative analgesia after intravenous methadone in comparison with intravenous morphine in children aged 3–7 years. During the first 36 hours after surgery, the group receiving methadone required less supplemental analgesia and reported lower pain scores. No major adverse effects occurred in either group.[32] Another randomised trial found that methadone produced significantly greater ventilatory depression than morphine or pethidine, although the risk of clinically significant hypoventilation was small.[33] The incidence of other side effects including nausea, vomiting, and urinary retention was the same in all three treatment groups.

Potential for use of methadone in newborns

Although these studies into the pharmacokinetics, analgesic potency, and side effect profile of methadone in children give an indication of what to expect with the use of methadone in neonates, these results cannot be extrapolated for neonatal treatment. Age has an important influence on the pharmacokinetics of opioid analgesics.[34] Previous studies of other analgesics suggest that elimination of the drug from the body is slower in neonates than in older children or adults. Methadone has greater lipid solubility and protein binding capacity than morphine, which may explain the larger volume of distribution and a slower clearance.[35] Neonates born at term have more adipose tissue and higher plasma protein levels than preterm neonates, which may significantly alter drug distribution and metabolism.

Rough estimates of neonatal methadone metabolism are only available from the monitoring of plasma levels in neonates born to methadone addicted mothers, although these are not true pharmacokinetic studies. Rosen and Pippenger[36] found that the plasma half life of methadone was 16–25 hours in groups of neonates (gestational age 34–43 weeks) showing different degrees of opioid withdrawal. These authors noted that the pronounced individual variability in neonatal methadone metabolism was not related to the maternal dose of methadone and that neonates with plasma levels higher than 0.06 µg/ml did not show any signs of opioid withdrawal. Conflicting results were reported by Mack *et al*,[37] who found a mean (SD) elimination half life of 41 (22) hours, indicating slower plasma clearance for methadone in these infants. Both studies, however, were complicated by unreported maternal ingestion of methadone, exposure to other drugs of abuse during pregnancy, and variable intervals between the last dose of methadone and delivery.

In view of the physicochemical, pharmacological, and therapeutic properties of methadone noted above and its usefulness in adult patients, we propose that there is an urgent need for clinical studies of the use of methadone analgesia in neonates. The benefits of methadone include potent analgesic effects, prolonged duration of action, delayed development of opioid tolerance, excellent enteral bioavailability, and its low cost in relation to other opioid analgesics. However, therapeutic protocols using methadone cannot be defined without data on its pharmacokinetics and pharmacodynamics in neonates. In addition, the need for clinical data on its immediate safety and long term developmental effects following use at different gestational ages requires that methadone use be limited to carefully designed research protocols, and perhaps only in specialised centres. The available evidence thus far suggests a prominent therapeutic role for this new "old" drug in the management of prolonged neonatal pain.

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Commentary

Opiates have been routinely used in adult and paediatric intensive care for many years, particularly for ventilated patients. They are given for their analgesic properties; separate drugs are used for sedation and muscle relaxation. Use of opiates has now spread to neonatal intensive care, because ventilated infants are physiologically more stable and hormonally less stressed when receiving an opiate infusion.[1][2] The opiate is used for both its analgesic and sedative properties; pure sedatives and muscle relaxants are rarely used. Opiates are also used for postoperative analgesia and for the treatment of withdrawal symptoms in infants of opiate addicts. They have never been subjected to a randomised controlled trial of long term outcome and safety in the newborn (neither have opiates in adult and paediatric intensive care), but short term outcome measures are improved.[3] Morphine and diamorphine are the most commonly used opiates in the United Kingdom, and there is now considerable experience of their use. Tolerance and physical dependence are not usually seen because the drugs have a long half life and are given for short periods. Hypotension is described but the small fall in blood pressure may be a result of effective analgesia rather than an unwanted side effect.[4–6] Most of the concerns of Chana and Anand relate to the short acting synthetic opiate fentanyl. Although the most commonly used opiate in North America, its use in the United Kingdom is usually confined to operative and postoperative analgesia. Early onset of tolerance means that increasing doses are needed to achieve the same effect.[7] Dependence leading to withdrawal symptoms is well recognised with fentanyl,[8] as is the development of a "frozen" chest which impairs ventilation. These are good reasons for preferring morphine or diamorphine.

So why do we need another opiate? Well, it is always worth revisiting an old drug for a new use and sometimes more rewarding than exploring new drugs. Chana and Anand suggest that we take a new look at methadone, an opiate largely used to suppress withdrawal symptoms in addicts who are trying to come off heroin. If the addict is a pregnant woman, this is probably the only way that a newborn infant will receive the drug at present. Although methadone may help the mother's addiction, there is a common perception that withdrawal symptoms in the newborn are more severe with methadone than with heroin. However, this is not a situation that would mimic the therapeutic use of methadone in the newborn and therefore no reason for not exploring it further.

Much experience of methadone is based on its oral use. An opiate that is well absorbed and therefore suitable for oral administration would be useful in newborn care. The ventilated infant is most easily managed with a continuous intravenous infusion but there are circumstances when the intravenous route is inconvenient, difficult, or even impossible. The management of opiate withdrawal, the long term ventilated infant, and the infant with a terminal disorder are examples. Oral morphine is available and widely used in children and adults, but its use in the newborn is mainly confined to the management of opiate withdrawal. It is relatively short acting and therefore needs to be given frequently, which limits its usefulness. Chana and Anand point out that oral methadone acts rapidly, with potent, long lasting analgesic effect. It therefore has important theoretical advantages over morphine. Before it can be used though, we need to know about the physiological and behavioural effects of methadone administration in the newborn and how it is eliminated, in both the term and preterm. Until this information is available, it should only be used in a research protocol.

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